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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,594	06/22/2000	Irina Nazarenko	0942.4980002/RWE/SEZ	8750

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EXAMINER	
FREDMAN, JEFFREY NORMAN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,594	NAZARENKO ET AL.	
	Examin r	Art Unit	
	Jeffrey Fredman	1634	

-- Th MAILING DATE of this communication appears on the cov r sheet with th correspond nce addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-22,47 and 56-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-22,47 and 56-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status

Claims 10-22, 47 and 56-67 are pending.

Claims 10-22, 47 and 56-67 are rejected.

1. Any rejection which is not reiterated in this action is hereby withdrawn as no longer applicable.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 10-22, 47 and 56-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

Here, the new limitation of "with the proviso that said one or more detectably labeled oligonucleotides do not comprise an acceptor molecule" in each of the independent claims appears to represent new matter. A careful review by the examiner of all of the cited pages in the specification failed to identify any support for this new

negative limitation. In fact, the phrase "acceptor molecule" was not found by the examiner in the specification.

As noted by MPEP 2173.05(I), " Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

In concert with Grasselli, it is noted that the specification does not even appear to have contemplated this exclusion. For example, the specification notes "[T]he label is any moiety which undergoes a detectable change in any observable property upon hybridization (see page 44, lines 4-6)". This quote expressly supports the position that the specification contemplated any label with any property, including a label which was an acceptor. Further supporting this position is the express statement on page 24, lines 15-16 that "In another embodiment of the invention, the label is a member of a FRET pair." Since one member of a FRET (fluorescence resonance energy transfer) pair must, definitionally, be an acceptor molecule, this quote also indicates that there was no possession of the idea that acceptors should not be permitted.

Since no basis has been found to support the new claim limitation in the specification, the claims are rejected as incorporating new matter.

4. Claims 10-22, 47 and 56-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by the term "acceptor" in the claims. In particular, there is no definition of this term in the specification and no mention of the term was even found in the specification. It is unclear what the scope of the term "acceptor" is with regard to this claim. While a Fluorescence resonance energy transfer as in Heller is clearly intended to be excluded, where the acceptor reemits the signal, it is unclear what other types of interactions fall within the scope of this proviso. For example, fluorescence quenching involves transfer of energy but given the focus of the specification on such transfer, it seems unlikely that this is intended to be excluded. However, because the term "acceptor" is used, and no definition is provided, it is indefinite whether a quencher falls within the scope of the restrictive proviso or not. Further, other elements such as intercalators or even some nucleotide bases may also serve as "acceptors" in some circumstances and it is indefinite what effect the proviso would have with regard to other "acceptors" since the term is not defined by the specification.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 10-17, 47, 56-58, 62, 64, 66, 67-70, 72 and 73 are rejected under 35 U.S.C. 102(b) as being anticipated by Livak et al (WO 96/15270).

Livak teaches a method for the quantitation of a target nucleic acid molecule in a sample (abstract and page 14, lines 14-16) comprising:

hybridizing one or more detectably fluorescently labeled oligonucleotides with one or more molecules to be detected or quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located internally (see page 14, lines 3-28 and page 30, "Hybridization assay using Oligonucleotide probe" and table 7, where Livak teaches hybridization involving the use of probes such as A1-7 which has an internal TAMRA) and said one or more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule (see page 10, lines 16-30, page 34, table 7, where Livak clearly shows that internally labeled probes A1-7, A3-6, P2-7, P510 all show a change in fluorescence between the single and double stranded states)

and quantifying the amount of the target nucleic acid molecules (see page 14, lines 3-28 and page 31, lines 4-6 "The magnitude of RQ indicates the level of hybridization of the A1-26 probe and thus is a measure of the amount of amplified beta-actin DNA segment captured in each well (so Table 7 which provides RQ data for internally labeled probes A1-7, A3-6, P2-7, P510 also measures the amount of target).

Livak expressly meets the proviso that the labeled oligonucleotides do not comprise an acceptor molecule but only involve quenching (see page 10, lines 16-18).

Livak expressly teaches monitoring of PCR amplification using the claimed probes (see page 15, lines 1-15) and exemplifies such a monitoring on page 32 (see subheading "Method for monitoring PCR amplification using oligonucleotide probe") which includes all the components necessary for PCR (see page 32).

Livak teaches the use of hairpin probes (see page 2).

Livak teaches placement of the label at the 3' end, as well as 5 nucleotides and 8 nucleotides from the 3' end (see page 22, probe A1).

7. Claims 18-22, 59-61, 66, 67 and 71 are rejected under 35 U.S.C. 102(b) as being anticipated by Nazarenko et al (Nucleic Acids Res. (1997) 25(12):2516-2521).

Nazarenko teaches a method for the quantification or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of: a) mixing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close (as close as seven nucleotides (see table 1)) to the 3' end respectively, wherein the oligonucleotide undergoes a detectable change in fluorescence upon hybridization to form the double stranded molecule (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4), b) incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template (page 2518, column 1 and figure 1), c) detecting the presence or absence, and quantifying the amount of synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

With regard to the proviso, Nazarenko teaches that the hairpin primers include a donor and a quencher (see page 2520, column 2) and, in view of the 112, second paragraph rejection above, for purposes of this rejection, the term "acceptor" is interpreted to be limited to the sort of acceptors used in Heller, which reemit the fluorescence energy for detection at a different wavelength.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 68-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al in view of Nazarenko et al.

Heller teaches a method for the detection of a target nucleic acid molecule in a sample (abstract and column 4) comprising:

hybridizing one or more detectably labeled oligonucleotides with one or more molecules to be detected or quantified, wherein said one or more oligonucleotides comprise one or more detectable labels located internally (see figures 2A, 2B, 3A, 3B and column 23, lines 15-29 for examples of oligonucleotides with detectable labels located internally which are also near the 3' or 5' termini) and said one ore more labels undergo a detectable change in an observable property upon becoming part of a double stranded molecule (see column 25, lines 62-66, where Heller shows that there is no energy transfer at 90 C, when there is no double stranded molecules but that upon cooling and rehybridization to reform the double stranded energy transfer system, there is a change in observable properties in that energy transfer is restored), and

detecting the presence or absence of one or more target nucleic acid molecules (column 17, line 45 to column 19, line 56) which may include a PCR amplification step thereby incubating the nucleic acid mixture to synthesize additional nucleic acid (see column 21, lines 32-35).

Heller teaches the use of Fluorescein and Rhodamine (see Table 2 and column 11).

Heller teaches the location of the acceptor fluorophore within 20 nucleotides of the 3' end (see column 23, line 15). Heller also shows the use of fluorescein, a detectable label, on column 26, line 24, which is 6 nucleotides from the 3' termini.

Heller does not teach the use of hairpin primers in the PCR reaction, nor does Heller teach placement of the fluorophores either four or five nucleotides from the 3' terminus.

Nazarenko teaches a method for the quantification or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of: a) mixing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close to the 3' end respectively, wherein the oligonucleotide undergoes a detectable change in fluorescence upon hybridization to form the double stranded molecule (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4), b) incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template (page 2518, column 1 and figure 1), c) detecting the presence or absence, and quantifying the amount of synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the Heller detection method using PCR with a hairpin primer as taught in the Nazarenko method since Heller states "A multiple donor system comprised of such non-fluorescent chromophores would have very little inherent fluorescent background. This property overcomes a major limitation that has severely limited practical uses of fluorescent energy transfer in DNA diagnostic assay applications (column 10, lines 23-27)". Thus, an ordinary practitioner using the Heller system is expressly motivated, in diagnostic applications, to reduce background using the Heller methodology and would be motivated to reduce background to as low a level as possible. Nazarenko provides motivation to combine with Heller, stating that "The

main advantage of this method is the generation of the fluorescent signal by the product itself, rather than by the hybridized probe, as in previous methods. This keeps background low and allows real-time quantification of the amplified DNA over an extremely wide dynamic range (page 2521, column 1)".

Thus, an ordinary practitioner seeking to achieve a system with as minimal a background as possible for diagnostic uses in order to detect nucleic acids associated with diseases or infections would have been motivated to use the primer of Nazarenko because Nazarenko expressly states that this primer keeps background low as desired by Heller, who uses multiple fluorophores to relay energy transfer to also keep background low. An ordinary practitioner would have been motivated to form such a multiple relay system of Heller, combined into the hairpin primer of Nazarenko, in order to yield an even further reduced background, thereby further improving the sensitivity and low background of the resultant assay, making it more suitable for detection of nucleic acids for diagnostic purposes.

11. Claims 18-22, 59-61, 63-67 and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nazarenko et al (Nucleic Acids Res. (1997) 25(12):2516-2521).

Nazarenko teaches a method for the quantification or detection of a target nucleic acid molecule in a sample (abstract) comprising the steps of: a) mixing a nucleic acid template with an oligonucleotide which comprises a hairpin and which comprises both fluorescein (or FAM) and DABCYL fluorescent labels which are at the 5' end and internal but close (as close as seven nucleotides (see table 1)) to the 3' end respectively, wherein the oligonucleotide undergoes a detectable change in

fluorescence upon hybridization to form the double stranded molecule (page 2517, table 1, page 2518, column 1 and figure 1, and page 2520, figure 4), b) incubating said mixture under conditions sufficient to synthesize one or more nucleic acid molecules complementary to the nucleic acid template (page 2518, column 1 and figure 1), c) detecting the presence or absence, and quantifying the amount of synthesized nucleic acid by measuring the detectable label (page 2518, column 1 and page 2520, figures 4-6).

With regard to the proviso, Nazarenko teaches that the hairpin primers include a donor and a quencher (see page 2520, column 2) and, in view of the 112, second paragraph rejection above, for purposes of this rejection, the term "acceptor" is interpreted to be limited to the sort of acceptors used in Heller, which reemit the fluorescence energy for detection at a different wavelength.

Nazarenko does not teach each possible location of the internal base.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to adjust the exact positioning of the bases near the 3' end, since the particular distance from the 3' end is a matter of routine optimization in the absence of any secondary consideration. As noted in *In re Aller*, 105 USPQ 233 at 235,

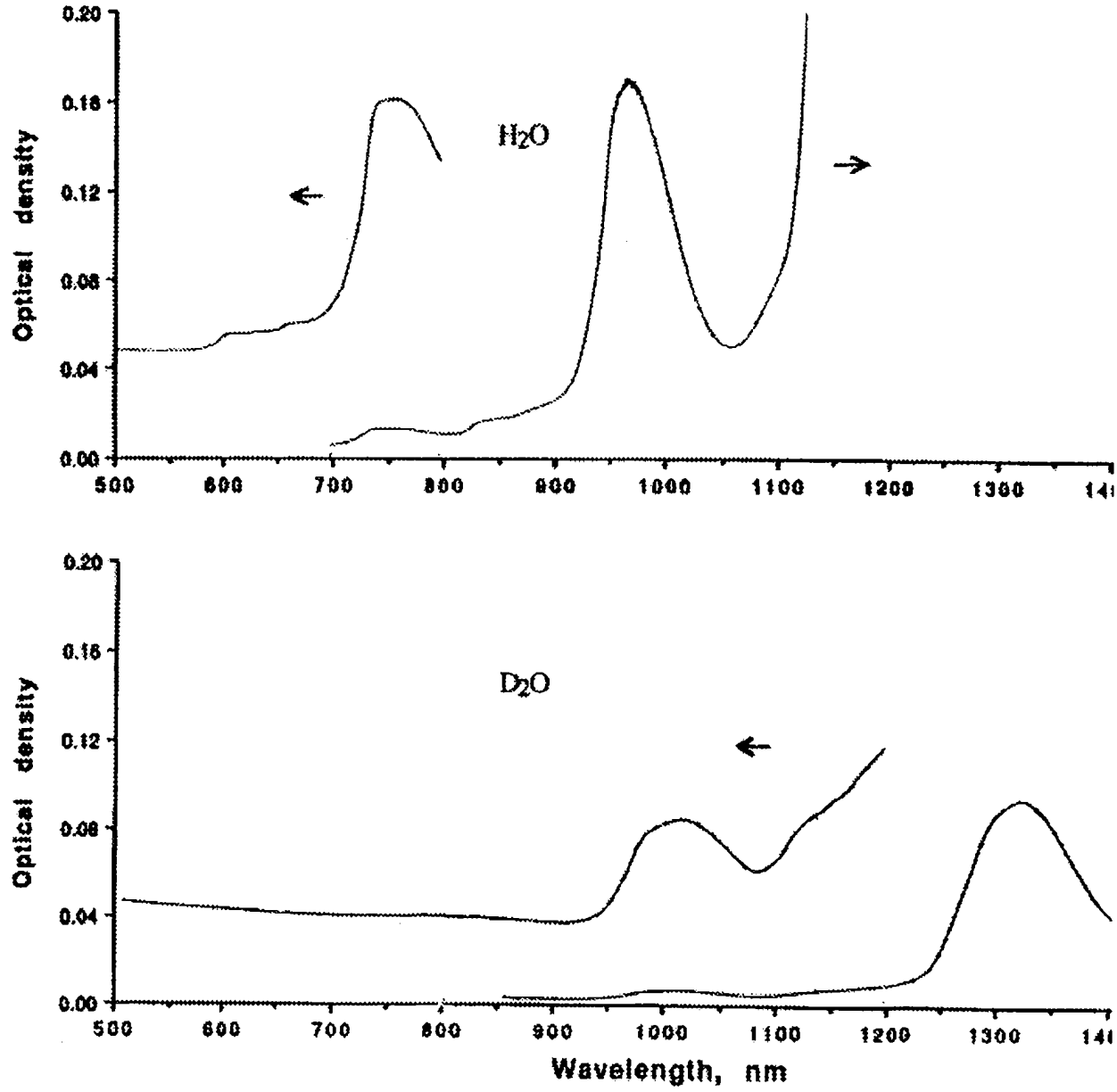
> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the specific positioning of the labels was other than routine and was unexpected in any way.

Response to Arguments

12. Applicant's arguments filed August 14, 2003 have been fully considered but they are not persuasive.

Applicant argues that the new, negative limitation in the claim does not constitute new matter. Applicant relies for basis for the new limitation on examples in which only a single label without an acceptor (see example 4 of the specification) as well as the generic statement that "the method does not require any specific quenching moiety" at page 70 of the specification. However, example 4 clearly shows that there is an increase in fluorescence in one state and a decrease in fluorescence in another state. This leads to the necessary conclusion that when there is a decrease in fluorescence, there must be some transfer to some acceptor in order to reduce the level of fluorescence. As shown in the figure below (derived from http://www.dartmouth.edu/~etrnsfer/water.htm), water itself adsorbs in the wavelengths between 500 and 600 nm, which is the range of emission of fluorescein, though peak absorption is at about 750 nm. Therefore, water itself functions as an "acceptor" in example 4, and the specification lacks any example where there is no molecule which can "accept" the emission. Water is noncovalently interacting with the oligonucleotide at all times in solution. Further, the DNA bases themselves may also function to accept a portion of the emissions, though given their significantly lower absorption wavelengths, at a very low level.



Consequently, the argument that there is no acceptor in example 4 is simply incorrect. This results in the conclusion that not only is there no literal support for the amendment, but there is no implied support, because the element being excluded is, in fact, present in the example that applicant argues as demonstrating exclusion. Some of the arguments that Applicant makes, such as "do not require the labeling with two

different compounds" are not currently in the claims. The claim does not have that exclusion but rather excludes the presence of any acceptor moiety, whether as a label, a nucleotide base or a non-covalently interacting component such as water.

Finally, the places cited in the action indicate that the specification contemplates FRET pairs and that this embodiment, unlike the embodiment argued by Applicant, is clearly described. There is no literal support for the negative recitation nor is there possession of this concept for the reasons given above and the new matter rejection is maintained.

Applicant then argues the 112, second paragraph rejection. Applicant reads the term as including anything which accepts energy, presumably therefore including water as discussed above. Applicant's arguments are not persuasive because the term is not defined in the specification. Applicant cites a number of references which purport to discuss the definition of acceptor. The claim does not even state what is being accepted. Why need it be fluorescent acceptance and not some other "acceptor" such as a chemical acceptor. However, the definition argued by the Applicant results in an absurd claim. Since the claim lacks any requirement that the "acceptor" that is absent is one which is related to the "donor", the DNA itself meets Applicant's post hoc definition of an "acceptor" as anything which absorbs energy. Therefore, the claim reads "detectably labeled oligonucleotides which do not comprise DNA", where DNA replaces the term "acceptor". Since there is no definition of the term "acceptor", Applicant's attempt to limit the term by reference to specific articles or places in the specification is not persuasive, since the proposed definition of Applicant results in uninterpretable

claims. Further, Heller clearly teaches a different definition of "acceptor" from Applicant, and no reason is provided why the definition currently desired by Applicant should be preferred to the definition provided by Heller.

Applicant then argues the prior art rejections based upon their specific definition of the term "acceptor". Because the indefiniteness of this term is maintained and Applicant's definition is not accepted, the prior art rejections of Livak and Nazarenko are maintained.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, specific motivation is provided in the rejection, where Heller states "A multiple donor system comprised of such non-fluorescent chromophores would have very little inherent fluorescent background. This property overcomes a major limitation that has severely limited practical uses of fluorescent energy transfer in DNA diagnostic assay applications (column 10, lines 23-27)". Thus, an ordinary practitioner using the Heller system is expressly motivated, in diagnostic applications, to reduce background using the Heller methodology and would be motivated to reduce background to as low a level as possible. Nazarenko provides motivation to combine with Heller, stating that "The

main advantage of this method is the generation of the fluorescent signal by the product itself, rather than by the hybridized probe, as in previous methods. This keeps background low and allows real-time quantification of the amplified DNA over an extremely wide dynamic range (page 2521, column 1)".

Conclusion

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is 703-308-6568. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634